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Atropine pharmacokinetics are affected by moderate hemorrhage and hypothyroidism

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Atropine is used both to treat a variety of clinical disorders and as an antidote to cholinesterase poisoning. While various conditions affect the physiologic responses to atropine, little is known of the pharmacokinetics of this drug except under resting conditions. Pharmacokinetic studies were performed in mongrel dogs under two experimental conditions, moderate hemorrhage and hypothyroidism, to determine whether im absorption and elimination of atropine (0.05 mg/kg body weight) were affected by changes in hemodynamic or metabolic status. Using a randomized, crossover experimental design, it was found that during hypovolemia the mean volume of distribution was reduced by 22% (2.50 ± 0.62 vs. 3.21 ± 0.63 L/kg), with no changes in peak serum level, total atropine availability, elimination half-life, or whole-body clearance. Hypothyroidism was associated with a significant increase in peak serum atropine concentration (26.4 ± 3.9 vs. 20.6 ± 4.9 ng/ml) and drug bioavailability (48.5 ± 8.8 vs. 30.0 ± 10.7 ng/ml·h), while the clearance was reduced by 39% (426 ± 34 vs. 696 ± 187 ng/ml·min). These results suggest that atropine kinetics are not altered appreciably during moderate hemorrhage. In hypothyroidism, alterations in atropine pharmacokinetics may warrant modification of drug dose and frequency of administration. (Crit Care Med 1989; 17:1254)

Atropine, an anticholinergic drug, is widely used as a preanesthetic medication, for bradycardic syndromes, in the treatment of some ophthalmic disorders, as a component of decongestant medications, and as an antidote to certain anticholinesterase toxins. As an antidote, atropine is the treatment of choice for patients affected by chemical warfare nerve agents, and it may be used as a treatment (for self-administration with pralidoxime) by military troops facing the threat of nerve gas attack.

The pharmacodynamics of atropine sulfate have previously been studied and its effects on certain physiologic responses (heart rate, mydriasis, inhibition of sweating) are known (1–5).

A number of situations alter an individual's physiologic responses to atropine. These include: a hot, dry climate (2); prior exercise (2, 6); hypovolemia (7); coadministration of pralidoxime (8); and enclosure in a nuclear, biologic, and chemical (NBC) suit (9). Other conditions which, although untested, may influence the response to a fixed dose of atropine are: a) extreme differences in body weight, b) fever, and c) metabolic disorders. It is not known whether these alterations reflect differences in drug bioavailability or in altered pharmacology.

Because renal excretion normally accounts for the major metabolic clearance of atropine (10, 11), and is likely to be depressed during circulatory shock, it is important to determine whether hypovolemia causes increased side-effects from doses of atropine recommended for normovolemic individuals. Therefore, we examined the pharmacokinetics of atropine in both euvolemic and hemorrhagic states. The importance of this study relates to the fact that in conditions utilizing chemical warfare agents, atropine would likely be given to patients suffering from acute hemorrhage. A second objective of this study was to determine whether atropine kinetics are influenced by hypothyroidism, a condition known to affect the metabolism of numerous drugs (12).

MATERIALS AND METHODS

Studies were performed on eight male mongrel dogs with a mean weight of 22.5 kg. On the day before the study, the animals had food withheld after 8:00 PM, but were allowed free access to water.

After anesthesia with a thiobarbiturate analog of secobarbital (Bio-Tal Thiamylal Sodium, Bio-Centric Laboratories, St. Joseph, MO), indwelling catheters were inserted percutaneously into a femoral artery. This arterial catheter was used for serial blood sampling and for monitoring mean arterial pressure (MAP). An indwelling venous catheter was inserted into a forelimb

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vein to allow for drug administration and was kept open by using an infusion (5 ml/h) of 0.9% saline.

Using a randomized crossover design, each dog was studied in both the normovolemic and hypovolemic states with an average rest of 14 days between studies. In normovolemic studies, two readings of heart rate (HR) and MAP were obtained over a 30-min baseline period. Atropine sulfate (0.05 mg/kg body weight im) was administered in the flank at the end of the baseline period.

In the hypovolemic study, as in the normovolemic study, baseline HR and MAP were obtained twice over 30 min. Animals were then bled (20 ml/kg) into a blood collection bag over a 60-min period and atropine was administered im 30 min into the bleed. Animals were retransfused (with their shed blood) 1.5 h after atropine administration.

Six animals subsequently underwent surgical thyroidectomy performed under general anesthesia 3 wk before their study. To assure that the animals were hypothyroid postoperatively, we performed thyrotropin (Thytropar, Armour Pharmaceutical, Kankakee, IL) stimulation tests before and after surgery. Serum thyroxine (T_4) concentrations were measured by radioimmunoassay using a kit (Canine T_4, Diagnostic Products, Los Angeles, CA) on serum obtained before and 6 h after im thyrotropin (10 IU) administration (13).

Blood samples (2.0 ml each) for atropine measurements were obtained immediately before, at 2, 3.5, 5, 7.5, 10, 15, 30, and 45 min, and at 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, and 6 h after atropine administration. BP and HR were recorded at each sampling time.

Serum atropine sulfate concentrations were measured by radioimmunoassay, similar to that of Wurzburger et al. (14), as previously described (15, 16). Sensitivity of the assay was 50 pg per tube (1 ng/ml). Intra-assay and interassay variation coefficients are 9.0% and 12.8%, respectively. The metabolites tropine and trophic acid do not react with this antibody.

Serum drug levels were fitted to a multiexponential function using a modified Marquardt technique for nonlinear regression (17). In each instance, the "best fit" model was determined by visual fit of the data to the various regimen models, and by the most significant r^2 and f ratio. Pharmacokinetic parameters measured included the elimination half-life, volume of distribution (Vd), total clearance, area under the drug time-concentration curve (AUC), and peak serum atropine concentration. Differences between treatments were determined to be significant at $p < .05$ by Student's paired t-test using the Bonferroni correction for multiple comparisons (18).

RESULTS

Hypovolemia

In normovolemic animals, atropine administration produced a significant 14% increase in HR (Table 1). Similarly, there was a 10% atropine-induced increase in MAP ($p < .05$).

In hypovolemic animals, mean maximum HR increased by 20% and BP increased by 10% during the first 30 min of bleeding before atropine administration (Table 1). At the time atropine was given, these variables had returned to near normal. After atropine administration, HR increased by 32% and MAP increased by 7%.

Pharmacokinetic data are illustrated in Table 2. There was a significant decrease in Vd in the hypovolemic dogs. No other parameter, including peak serum concentration, half-life, clearance, or AUC, was significantly affected.

TABLE 1. Hemodynamic measurements after atropine administration in dogs during hypovolemia and hypothyroidism (mean ± SD)

	Heart Rate (beat/min)		
	Baseline	Peak Hypovolemia	Peak Atropine
Hypovolemic Study (n = 8)			
Normovolemic	176 ± 11	N/A	200 ± 7[a]
Hypovolemic	145 ± 9	174 ± 6[a]	196 ± 8[a]
Thyroidectomy Study (n = 6)			
Euthyroid	166 ± 12	N/A	197 ± 7[a]
Hypothyroid	108 ± 19[b]	N/A	171 ± 7[a,b]
	Mean Arterial Pressure (mm Hg)		
Hypovolemic Study			
Normovolemic	158 ± 7	N/A	173 ± 5[a]
Hypovolemic	140 ± 13	154 ± 17[a]	149 ± 12
Thyroidectomy Study			
Euthyroid	156 ± 6	N/A	174 ± 6
Hypothyroid	133 ± 10	N/A	180 ± 8[a]

N/A, not applicable.
[a] $p < .05$ compared to baseline; [b] $p < .05$ compared to euthyroid.

Hypothyroidism

Serum T_4 (mean ± SD) was 2.5 ± 0.9 μg/dl in the euthyroid dogs, and increased to >6 μg/dl ($p < .05$) after thyrotropin in all animals. In the hypothyroid state, serum T_4 was 0.3 ± 0.1 μg/dl both before and after thyrotropin.

Hypothyroidism was associated with a significant reduction in resting rate (Table 1). While the peak HR achieved after atropine was also reduced (171 ± 7 vs. 197 ± 7 beat/min), the percentage increase from baseline was actually greater in the hypothyroid animals. The MAP was 15% lower basally in the thyroidectomized animals, but reached levels comparable to the euthyroid state after atropine.

Hypothyroidism was associated with multiple changes in the kinetic parameters of atropine (Table 3). These changes included a significant reduction in the drug's clearance, and increases in peak serum concentration (Fig. 1) and AUC. The mean half-life was prolonged by 62%, but this change was not statistically significant. The Vd was unchanged.

DISCUSSION

The current study was designed to examine the effect of acute, moderate hemorrhage on atropine sulfate absorption, and elimination from an im site. An earlier study in cats (7) suggested impaired absorption into the circulation if atropine was given subcutaneously (blood levels were not reported).

In the current experimental model, moderate hemorrhage led to temporary tachycardia and an increase in MAP, probably through activation of the sympathetic nervous system (19) and vasoconstriction.

Pihlajamaki et al. (20) demonstrated that sodium nitroprusside-induced hypotension in anesthetized man does not impair im absorption of atropine. They speculated that drug-related hypotension (unlike hemorrhage) may not impair peripheral tissue perfusion, thus accounting for a lack of effect on atropine metabolism. Hypotension was not evident in our study, possibly due to splenic autotransfusion. The hemodynamic alterations observed suggest a compensatory response with a reduction in circulation to the peripheral vascular bed. The finding of a significant Vd decrease is consistent with these observations. Although other parameters (e.g., half-life) were unaltered, this fact may be due to maintenance of BP. From these results, we conclude that atropine bioavailability from an im site is not impaired during moderate hemorrhage, provided that BP is maintained.

Hypothyroidism may prolong a drug's half-life, prolong its clearance, or increase its blood level (12). Possible contributing factors include a reduced cardiac output, renal plasma flow, and hepatic drug metabolizing enzyme activity. Shenfield (12) noted that one cannot predict a priori the effect that thyroid dysfunction might have on a particular drug. There are several reasons for determining the effect of hypothyroidism on atropine kinetics. First, hypothyroidism occurs more commonly in elderly patients (21) and in association with a bradycardia. Second, patients with hypothyroidism have undergone successful general surgery and cardiac surgery before treatment with thyroid hormone (22–24). Since hospitalized hypothyroid patients might therefore receive atropine, either for bradycardia or as a preanesthetic medication, we decided to investigate the effect of hypothyroidism on the drug's metabolism.

The results of our study indicate that hypothyroidism delays atropine clearance and increases peak circulating blood levels. These experimental observations suggest that both the dose and frequency of atropine administration should be modified in clinical hypothyroidism.

TABLE 2. Atropine pharmacokinetics in male dogs (n = 8); effect of acute hemorrhage

	$T_{½\beta}$ (h)	Vd (L/kg)	Clearance (ng/ml·min)	AUC (ng/ml·h)	Peak Conc (ng/ml)
Normovolemic	2.1 ± 0.8	3.21 ± 0.63	638 ± 193	31.8 ± 9.8	21.0 ± 4.6
	(1.2–3.1)	(2.12–3.71)	(397–942)	(19.7–50.3)	(14.9–28.3)
Hypovolemic	1.7 ± 0.9	2.50 ± 0.62[a]	581 ± 154	33.8 ± 8.2	21.5 ± 4.2
	(0.8–3.1)	(1.57–2.85)	(410–794)	(21.0–48.5)	(15.8–26.5)

$T_{½\beta}$, elimination half-life; clearance, total body drug clearance; peak conc, peak serum atropine level. Numbers in parentheses indicate range.
[a] $p < .05$.

TABLE 3. Atropine pharmacokinetics in hypothyroid dogs (n = 6) (mean ± SD)

	$T_{½\beta}$ (h)	Vd (L/kg)	Clearance (ng/ml·min)	AUC (ng/ml·h)	Peak Conc (ng/ml)
Euthyroid	2.1 ± 0.8	3.31 ± 0.51	696 ± 187	30.0 ± 10.7	20.0 ± 4.9
	(1.2–3.1)	(2.75–4.14)	(397–942)	(19.7–50.3)	(14.9–28.3)
Hypothyroid	3.4 ± 1.6	3.17 ± 1.01	426 ± 34[a]	48.5 ± 8.8[a]	26.4 ± 3.9[a]
	(1.6–5.2)	(1.98–4.68)	(370–462)	(40.6–62.1)	(22.5–32.8)

See Table 2 for key to abbreviations. Numbers in parentheses indicate range.
[a] $p < .05$.

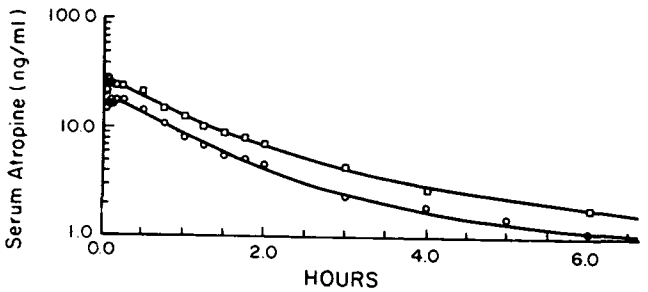

FIG. 1. Serum atropine levels measured in euthryoid (*circles*) and hypothyroid (*squares*) dogs from 2 min to 6 h after the im administration of atropine sulfate (0.05 mg/kg body wt). Each data point is the mean value of all six dogs. The Y-axis expresses the results on a log scale.

The route of atropine administration may affect the relevance of these results. In a combat situation involving trauma and hypovolemia, soldiers also exposed to nerve agents will receive atropine initially as an im injection. At that time, local tissue perfusion may be an important determinant of drug bioavailability. Once definitive medical care is available, additional atropine may be given iv, circumventing this potential problem. In the hypothyroid experiment, absorption from an im site was unimpaired, but systemic clearance was considerably delayed. Although hypothyroid patients in a hospital setting would most likely be given atropine by the iv route, the same alterations in drug clearance would be expected as observed in the present study.

In summary, this study has identified two conditions in which the pharmacokinetics of atropine may be altered. This information should be considered when atropine is given to certain patients.

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